conjugated to said nuclear targeting peptide via a chemical linkage.

8. (amended) A compound comprising:

(a) a cationic peptide scaffold; and

(b) a nuclear targeting peptide containing a non-classical nuclear localization sequence which does not interact with importin-α and importin-β, said cationic peptide scaffold being conjugated to said nuclear targeting peptide via a chemical linkage, wherein the nuclear targeting peptide comprises SEQ ID NO:1.

REMARKS

Claims 1-13 are pending in this application. Claim 14 has been canceled, without prejudice. Claims 1, 7 and 8 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Finality of Restriction Requirement

The Examiner has made final the Restriction Requirement. Accordingly, in an earnest effort to advance the prosecution of

this case, Applicant has canceled claim 14, without prejudice. In light of the finality of this Restriction Requirement, however, Applicant reserves the right to file a divisional application to the canceled subject matter.

II. Priority of Invention under 35 U.S.C. § 119

The Examiner suggests that Applicant has not complied with one or more of the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119, in that the present application does not contain a specific reference to the prior application in the first sentence of the specification or in an application data sheet. Applicant has amended the specification to include specific reference to the prior applications, and recite the priority date for the instant application as that of U.S. Provisional Application No. 60/098,791 filed September 1, 1998. This priority claim is supported by the executed Declaration and Power of Attorney filed in the instant application. No new matter is added by this amendment.

III. Objection to Claim 1

The Examiner has objected to claim 1 as being grammatically incorrect. Specifically the Examiner suggests that the phrase "a eukaryotic cells" should be amended. Accordingly, Applicant has amended claim 1 to be grammatically correct to recite "a eukaryotic cell". Applicant respectfully requests withdrawal of this objection in light of this amendment.

IV. Rejection of Claims 1-11 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-11 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner suggests that claims 1-3 are indefinite because it is unclear what is intended by the term "enhancing". Accordingly, in an earnest effort to advance the prosecution of this case Applicant has amended claim 1 to remove this term.

The Examiner also suggests that claims 1-11 are indefinite because it is unclear what is encompassed by the phrase

"nonclassical nuclear localization signal". Applicant respectfully disagrees.

As taught at page 5, lines 2-19, of the application "classical nuclear localization signals" are peptide sequences of clustered residues that interact with two proteins, importin-α and importin-β, also known as karyopherin α and karyopherin β, respectively. In contrast, as taught at page 8, lines 12-17, the non-classical nuclear localization signals do not interact with proteins such as importin-α and importin-β. Accordingly, Applicant believes that one skill would understand what is meant by nonclassical nuclear localization signal in light for the teachings of the specification. However, in an earnest effort to advance the prosecution of this case, Applicant has amended the claims to clarify that nonclassical nuclear localization signals do not interact with importin-α and importin-β.

The Examiner also suggests that claims 7 and 8 are indefinite as it is unclear what is intended by "hydrolytic resistant". The Examiner suggests that the claim requires a hydrolytic resistant chemical linkage, but it is unclear how the limitation resistant is intended to modify the claim. Accordingly, in an earnest effort to advance the prosecution of this

application, Applicant has amended claim 7 to remove the term "hydrolytic-resistant".

Withdrawal of the rejections of claims 1-11 under 35 U.S.C. §112, second paragraph, is respectfully requested in light of these claim amendments.

V. Rejection of Claims under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-7 and 9-13 under 35 U.S.C. § 102(b) as being anticipated by Thatcher et al. (WO 96/41606 published 12/27/96). The Examiner suggests that Thatcher et al. teach a composition comprising a cationic peptide scaffold (NBC2, page 8, line 20), the nuclear localization targeting peptide encoded by SEQ ID NO:3 of the instant invention (M9, comprising the NLS of hnRNP A1) wherein the scaffold and the targeting peptide are conjugated by a hydrolytic resistant linkage. The Examiner also suggests that the composition is taught as useful in methods of transferring DNA to nuclei of cells and subsequently expressing encoded genes.

Applicant respectfully traverses this rejection.

Claims of the instant application are explicitly drawn to nuclear targeting peptides containing a **nonclassical**, nuclear localization signal. In contrast, the section cited by the

Examiner in Thatcher et al. relating to NBC2 shows the structure of NBC2 to contain a **classical** nuclear localization signal SV40 NLS1 (see page 8, lines 12-13 of Thatcher et al.). The composition taught at page 92 of Thatcher et al. which contains both NBC2 and M9 also contains a **classical** nuclear localization signal. Accordingly, the compositions taught in WO 96/41606 are different from the compositions claimed in the instant application.

Further, Applicant respectfully disagrees with the Examiner's suggestion that WO 96/41606 teaches these compositions to transfer DNA to the nuclei of cells. No experiments using the composition of NBC2-M9 are disclosed in WO 96/41606. In fact, it is questionable whether the proposed method of synthesis could actually even result in this composition as M9 is known to form dimers under such conditions. Further, as taught at page 5, lines 20-26, of the instant application, classical nuclear localization signals such as the SV40 T antigen have **not** been able to get plasmid across the nuclear pore of intact cells. Thus, without some demonstration of actual activity, it is completely unpredictable whether the NBC2-M9 composition containing both a classical and a nonclassical nuclear localization signal would successfully

transfer DNA to the nuclei of cells. Accordingly, the teachings of WO 96/41606 do not anticipate the instant claimed invention.

The Examiner has further rejected claims 1-7 and 9-13 under 35 U.S.C. 102(b) as being anticipated by Jans et al. (Med. Res. Rev. 1998). The Examiner suggests that Jans et al. teach that polypeptides comprising SEQ ID NO:3 may be chemically crosslinked to cationic DNA binding proteins for delivering DNA to the nuclei of cells. Applicant respectfully disagrees.

At the outset, it is respectfully pointed out that the Jans et al. reference, which published in July 1998, is improperly cited as a §102 (b) reference. The priority date of the instant application is September 1, 1998. The specification has been amended herein to include the proper statement to receive the benefit of this earlier filing date. Accordingly, since Jans et al. did not publish more than one year from the September 1, 1998 priority date of the instant application, this reference can not be cited under 35 U.S.C. §102 (b).

Further, Jans et al. is a review article summarizing recent progress in the understanding of signals mediating the transport of proteins through the nuclear pore complex. Nowhere is the chemical cross-linking of a polypeptide comprising SEQ ID NO:3 to cationic DNA binding proteins for delivering DNA to the nuclei of cells

actually taught or suggested by Jans et al. In fact, Jans et al. places M9 in a separate category of NLSs which they refer to as "shuttle signals". See page 192. Further, at page 215, Jans et al. state that shuttle sequences may be used in conjunction with prNLSs but only to ensure that nuclear targeting is precisely scheduled and only when the parameters modulating their directionality are understood and able to be manipulated. Thus, nowhere is it taught or suggested in this reference to use a nonclassical nuclear targeting sequence such as M9 alone to deliver a DNA plasmid to the nuclei of a cell. Nor does this reference provide any reasonable expectation that a "shuttle signal" such as M9 alone could be used to successfully deliver a DNA plasmid to the nuclei of a cell. Accordingly, the claims are not anticipated by the teachings of Jans et al.

Withdrawal of these rejections under 35 U.S.C. §102 (b) is therefore respectfully requested.

VI. Amendment to Claim 8

The Examiner has stated that claim 8 has been found to be free of prior art of record. Accordingly, Applicant has amended claim 8 to present the claim as an independent claim. Allowance of this claim is respectfully requested.

VII. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment, captioned "Version with Markings to Show Changes Made".

Respectfully submitted,

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Date: **August 22, 2002**

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 14 has been canceled.

Claims 1, 7 and 8 have been amended as follows:

1. (amended) A composition for ~~enhancing~~ delivery of a molecule to the nucleus of a eukaryotic cell comprising a nuclear targeting peptide containing a nonclassical, nuclear localization signal.

7. (Amended) A compound comprising:

(a) a cationic peptide scaffold; and

(b) a nuclear targeting peptide containing a non-classical nuclear localization sequence,

said cationic peptide scaffold being conjugated to said nuclear targeting peptide via a ~~hydrolytic-resistant~~ chemical linkage.

8. (Amended) ~~The compound of claim 7~~ A compound comprising:

(a) a cationic peptide scaffold; and

(b) a nuclear targeting peptide containing a non-classical nuclear localization sequence.

said cationic peptide scaffold being conjugated to said nuclear targeting peptide via a chemical linkage, wherein the nuclear targeting peptide comprises SEQ ID NO:1.